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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,861	02/02/2007	Jeroen C. Verheijen	34251-501 NATL	1084

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EXAMINER	
SOLOLA, TAOFIQ A	
ART UNIT	PAPER NUMBER
1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,861	VERHEIJEN ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-80* is/are pending in the application.

4a) Of the above claim(s) *66-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-65 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 54-80, are pending in this application.

Claims 1-53, are deleted.

Claims 66-74 are drawn to non-elected inventions.

Response to Restriction

The election of group I in the Paper filed 9/21/09 is hereby acknowledged. There is no indication if the election is made with or without traverse. Therefore, it is deemed made without traverse. The restriction is deemed proper and therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-79, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack adequate support in the specification. Increasing acetylcholinesterase and cholinergic deficiency are not a practical utility under US patent practice. To ascertain the practical utilities, one must read the specification into the claims contrary to several precedent decisions by the US courts and Official practice. Even then, the claims would become duplicates of 54-65, 80, and duplicates of each other. The claims are attempts by applicant to claim treatment of all diseases known today and that may be discovered in the future, arising from the Increasing acetylcholinesterase and cholinergic deficiency. They are reach-through claims and are no longer patentable under the US patent practice. Also, duplicates or substantial duplicate

claims cannot be in the same application under the US patent practice. A claim must stand alone to define the invention, and incorporation into the claims by reference to the specification or an external source is not permitted. *Ex parte Fressola*, 27 USPQ 2d 1608, BdPatApp & Inter. (1993). In patent examination, it is essential for claims to be precise, clear, correct, and unambiguous. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). By deleting the claims the rejection would be overcome.

Claims 54-65, 75-79, are drawn to all nervous system diseases known and those that may be found in the future because claims 75-79 are drawn to mechanism by which the instant compounds work in the body. There is no evidence the instant compounds would treat such diseases. The requirement of 35 USC 112, is not what is known or obvious to one of ordinary skill in the art but a "full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same", *Lookwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997). See also the status above.

Claims 54-65, 75-79, are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the claimed mechanisms and the diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, It is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. at 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement.'" *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed invention is not enabled without undue experimentation for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC, 1988): "The factors to be considered [in making an enablement rejection] have been summarized as a) the breadth of the claims, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and, the quantity of experimentation necessary, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex prate Formal*, 230 USPQ 546. The breadth of the claims includes many compounds. The compounds embraced by the claims are so numerous and are in the hundreds of thousands. The nature of the invention is using the compounds as pharmaceuticals. There is no known

prior art that broadly teaches treatment of all disorders arising from the mechanism cited in claims 75-79 and/or all nervous system diseases. No drug is known as one-size-fits-all in pharmaceutical industry. Many of the diseases are symptoms of Alzheimer but may also occur in many diseases other than Alzheimer. Treating a symptom such as dementia is not the same as treating the underlying disease and in fact is redundant. There is no evidence in the specification that instant compounds would treat all disorders arising from the mechanism cited in claims 75-79 and/or all nervous system diseases and all secondary diseases arising from sources other than Alzheimer disease.

The state of the prior art is that enzymes react in a lock and key mechanism and the structure of the compound must be specific. The presence of methyl instead of H changes the binding of a compound with an enzyme. For example, theophylline and caffeine differ by a methyl group but one is used as a bronchodilator while the other is not used as a pharmaceutical. Hence, there is no absolute predictability or established correlation between different substituents on a core that they would behave in a certain way. The uncertainty presents one of ordinary skill in the art with obstacles and prevents her from accepting any therapeutic regimen on its face. The level of ordinary skill in the art of pharmaceutical art is high. The level of unpredictability in pharmaceutical art is very high, e.g. theophylline v. caffeine. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The diseases listed in the claims are deemed speculations because there is no conclusive evidence that the instant compounds are applicable to all the claimed diseases. There is no correlation between the assays disclosed in the specification and each disease. On page 67, applicant listed six tested compounds. The compounds are not sufficient representations of the

instant compounds. While IC_{50} are reported for the six tested compounds, there are no explanations of the results linking the results with each claimed disease. Given the limited guidance in the specification one of ordinary skill in the art would have to perform significant amount of experiments to make and use the invention as claimed.

It is quite possible that a mutation in the gene for the protein responsible for cholinesterase production may lead to decreased levels. To use the invention as claimed, one of ordinary skill in the art would have to perform experimentation in every instance to determine if the decrease is due to genetic mutation in a patient or not. After prospective patients are identified and treated, assays must be performed on each one to determine if treatment is successful. However, the specification fails to disclose a routine procedure to perform such assays. Therefore, to make and use the instant invention, one of ordinary skill in the art would have to perform significant amount of experimentations. Such is deemed undue experiment under the US patent practice.

There are no disclosures in the specification establishing a link between the activities of the instant compounds and each of the claimed diseases. There is no absolute predictability or established correlation between the claims and the specification disclosures. The uncertainty presents one of ordinary skill in the art with obstacles and prevents her from accepting the invention on its face. Predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In the instant invention, there is no direction or guidance by applicant because assays are not performed for establishing nexus between the assays' results and each disorder. The specification cites several references but none of the references disclosed conclusive evidence of relationships between the mechanisms and all disorders arising therefrom. Therefore, there is no evidence in the

specification that established correlation between the disclosure and the instantly claimed invention. *See Ex parte Mass*, 9 USPQ2d 1746, (1987).

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding any of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. By limiting the disease to Alzheimer the rejection would be overcome.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 54-65, 75-79, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For the reasons set forth above under 35 USC 112, first paragraph the claims are indefinite. See the Examiner's suggestions above.

Claims 75-79 are duplicates when the claims are read in light of the specification. The term "combination" in every occurrence is subject to more than one interpretation and therefor renders claims 54-65, 75-80 indefinite. For example, the term could mean combination of the substituents to form a ring.

The specification discloses prior arts in support of the mechanisms and the diseases. However, the cited prior arts are not incorporated in accordance with the MPEP. See MPEP 608.01(p) and 37 CFR 1.57(b)(1). Applicant should note that enablement requirement is an 'essential material'. See 37 CFR 1.57(c), 1.57(c)(1) to (3). See also the MPEP 608.01(p), which states as follows:

A mere reference to another application, publication or patent is not an incorporation of anything therein into the application containing such reference for the purpose of satisfying the requirement of 35 USC 112, first paragraph. *In re de Seversky,* 474 F.2d 671, 177 USPQ 144 (CCPA 1973). Particular attention should be directed to the subject matter and the specific portions of the referenced document where the subject matter being incorporated may be found.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Jean-Pierre et al. FR 2 719 047.

The prior is applied as set forth in the Int. Search Report of Pct/US04/034548. See also, pp. 1-3, examples on pp. 17-25 and the claims.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Sandoz-Patent-gambH, DE 3805744 A1.

The prior is applied as set forth in the Int. Search Report of Pct/US04/034548. See also, the examples on pp. 2-3.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Terni et al. WO 96/02524.

Terni et al. disclose similar compounds and their method of use for treating nervous system diseases. See pp. 1-10 and examples 1-28.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Amstutz et al. Helvetica Chimica Acta (1990), Vol. 73, pp. 739-753.

Amstutz et al. disclose similar compounds and their method of use for treating nervous system diseases. See the abstract and compounds 2 and 7.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Rampa et al. J. Am. Chem. (2001), Vol. 44, pp. 3810-3820.

Rampa et al. disclose similar compounds and their method of use for treating nervous system diseases. See the introduction, Charts 1-2, pp. 3810, and compounds 13-14 on pp. 3811.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Goto et al. JP 30022155.

Goto et al. disclose similar compounds and their method of use for treating nervous system diseases. See compounds 1-2.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Enz, US 5,602,176.

Enz discloses similar compounds and their method of use for treating nervous system diseases. See compounds I and I'.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 102(b) as being anticipated by Rosin et al. US 4,948,807.

Rosin et al. disclose similar compounds and their method of use for treating nervous system diseases. See compounds 1-2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54-65, 75-80, are rejected under 35 U.S.C. 103(a) as being unpatentable over the prior arts listed above.

Applicant claims method of using the elected compounds for treating nervous system diseases.

Determination of the scope and content of the prior art (MPEP 2141.01)

The prior arts disclose similar compounds, their composition and method of use for treating nervous system diseases.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of the prior arts is that the alky chain in the compounds of Applicant is longer than in the prior arts. In other words, applicant replaced H with alky in the compounds of the prior arts. Also, applicant claims alkyl substituents instead of H by the prior arts and vice versa.

Finding of prima facie obviousness---rational and motivation (MPEP 2142.2413)

However, H and alkyl are art recognized equivalents. *In re Lincoln*, 126 USPQ 477, 53 USPQ 40 (CCPA, 1942); *In re Druey*, 319 F.2d 237, 138 USPQ 39 (CCPA, 1963); *In re Lohr*, 317 F.2d 388, 137 USPQ 548 (CCPA, 1963); *In re Hoehsema*, 399 F.2d 269, 158 USPQ 598 (CCPA, 1968); *In re Wood*, 582 F.2d 638, 199 USPQ 137 (CCPA, 1978); *In re Hoke*, 560 F.2d 436, 195 USPQ 148 (CCPA, 1977); *Ex parte Fauque*, 121 USPQ 425 (POBA, 1954); *Ex parte Henkel*, 130 USPQ 474, (POBA, 1960).

When the difference between compounds is the length of a carbon chain such are adjacent homologs. However, adjacent homologs are prima facie obvious. *In re Henze*, 85 USPQ 261 (1950). Therefore, the instant invention is prima facie obvious from the teaching of the prior arts. One of ordinary skill in the art would have known to replace H with alkyl or vice

versa at the time the invention was made. The motivation is from knowing that H and alkyl are equivalents and that adjacent homologs would have similar biochemical properties.

Alternatively, given the teachings of the prior arts and well known knowledge in the art, it would have been obvious to try replacement of H with alkyl or vice versa at the time the invention was made.

When there is motivation

> to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under [35 USC] 103.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct 1727, 82 USPQ2d 1385, 1397 (2007).

Alternatively, applicant has done nothing more than substitutes known equivalents in the prior arts' compounds. However, such substitution is obvious from the prior arts and knowledge in the art. "When a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *United States v. Adams,* 383 U.S. 49, 50-51 (1966). Cited in *KSR Int. Co. v. Teleflex Inc*, 550 U.S. ----, 82 USPQ2d 1385 (2007). The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR, supra.*

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

/Taofiq A. Solola/

Primary Examiner, Art Unit 1625

November 18, 2009